doi: 10.18484/2305-0047.2018.5.547

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INTRINSIC COAGULATION CASCADE FACTORS AND HEMOSTATIC MARKERS OF ENDOTHELIAL DYSFUNCTION IN PATIENTS WITH PERIPHERAL ARTERY DISEASE

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Цель. Оценка активности факторов внутреннего каскада коагуляции и гемостатических маркеров дисфункции эндотелия у пациентов с облитерирующим атеросклерозом артерий нижних конечностей (ОААНК) до и после эндоваскулярных вмешательств.

Материал и методы. В исследование было включено 80 пациентов с ОААНК IIБ-III стадии по А.В. Покровскому-Фонтейну. 40 пациентов с ОААНК подверглись эндоваскулярным вмешательствам на аорто-бедренно-подколенном сегменте (группа А), и 40 пациентов прошли консервативное лечение (группа В). Пациентам было проведено физикальное обследование, ультразвуковая допплерография (УЗДГ), дуплексное сканирование (УЗДС)/рентгеноконтрастная ангиография артерий нижних конечностей. Через 3 и 6 месяцев после проведенного лечения пациенты повторно прошли физикальное обследование, УЗДГ и УЗДС артерий нижних конечностей. При включении пациентов в исследование и через 3 месяца после операции были взяты образцы венозной крови для оценки активности факторов VIII, IX, XI, фактора фон Виллебранда (ФВ), оксида азота II (NO) и протеина С (ПрС).

Результаты. У пациентов группы А до оперативного вмешательства средние значения активности VIII, IX, XI факторов и ФВ были повышены по сравнению с нормой. Через 3 месяца после операции наблюдался еще больший рост активности VIII, IX, XI факторов, сохранялся повышенный уровень ФВ при снижении показателей метаболитов NO. У пациентов группы В были повышены средние значения активности IX, XI факторов, ФВ при нормальном уровне метаболитов NO и ПрС.

Заключение. Анализ исходного состояния системы гемостаза у пациентов с ОААНК позволяет сделать вывод о развитии гиперкоагуляционного состояния на фоне нормального антикоагуляционного потенциала. Оперативное вмешательство способствует еще большему сдвигу в сторону гиперкоагуляции и нарушению функционального состояния эндотелия.

Ключевые слова: атеросклероз, внутренний каскад коагуляции, гемостатические маркеры дисфункции эндотелия, оксид азота II, фактор фон Виллебранда

Objective. To assess the activity of intrinsic coagulation cascade factors of coagulation and hemostatic markers of endothelial dysfunction in patients with atherosclerotic peripheral artery disease (PAD) before and after endovascular treatment.

Methods. The study included 80 patients with PAD in the stage IIB-III of the disease according to Pokrovsky-Fontaine classification. 40 patients with PAD underwent endovascular interventions on the femoropopliteal segment (group A) and 40 patients underwent the conservative treatment (group B). Patients underwent physical examination, ankle-brachial index measurement (ABI), duplex ultrasound (DUS) and digital substraction angiography. 3 and 6 months after treatment patients underwent the same procedures. At inclusion of patients in the study and 3 months after the surgery, peripheral venous blood samples were collected to assess the activity of VIII, IX, XI, von Willebrand factor (VWF), protein C (PrC) and metabolites of nitric oxide II (NO).

Results. In patients of the group A mean values of activity VIII, IX, XI factors and VWF were increased in comparison with the norm before the surgery. After 3 months the results shown a greater increase in activity VIII, IX, XI factors, the elevated levels of VWF remained in the reduction of NO metabolites. In patients of the group B the mean activity values of IX, XI factors and VWF were increased with normal levels of NO metabolites and PrC.

Conclusions. The analysis of the initial state of the hemostasis system in patients with atherosclerotic peripheral artery disease allows us to conclude that the hypercoagulable state develops against the background of a normal anticoagulation potential. Operative procedures provide a further shift towards a hypercoagulable state and impaired functional activity of endothelium.

Keywords: atherosclerosis, intrinsic coagulation cascade, hemostatic markers of endothelial dysfunction, nitric oxide II, von Willebrand factor

Novosti Khirurgii. 2018 Sep-Oct; Vol 26 (5): 547-554
Intrinsic Coagulation Cascade Factors and Hemostatic Markers of Endothelial Dysfunction in Patients with Peripheral Artery Disease
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Научная новизна статьи
У пациентов с облитерирующим атеросклерозом артерий нижних конечностей повышена активность VIII, IX, XI факторов, фактора фон Виллебранда на фоне сниженного уровня метаболитов оксида азота (II). Эндоваскулярные вмешательства способствуют еще большему сдвигу в сторону гиперкоагуляции и нарушению функционального состояния эндотелия, о чем свидетельствуют увеличенная активность ФВ, VIII, IX, XI факторов и сниженная – метаболитов NO.

What this paper adds
In patients with peripheral artery disease, the activity of VIII, IX, XI factor, von Willebrand factor is increased against a background of decreased level of nitrogen metabolites (II). Endovascular interventions contribute to an even greater shift towards hypercoagulation and disruption of the functional state of the endothelium, as evidenced by the increased activity of von Willebrand, VIII, IX, XI factors and decreased – NO metabolites.

Introduction

Obliterating atherosclerosis of the lower limbs arteries or atherosclerotic peripheral artery disease (PAD) is widespread throughout the world. The number of patients with the disease in the period from 2000 to 2010 increased from 164 million to 202 million people, in 3% of them a critical lower limb ischemia was identified [1]. The best result in patients with PAD is surgical treatment that provides a revascularizing effect, but does not eliminate the underlying cause of the disease [2]. Endovascular methods are considered as the first line of treatment in most cases and are gaining momentum compared to open methods of treatment. This can be explained both by the growing experience of these interventions and by the technological developments of more safe and effective endovascular devices. In Russia, the share of endovascular interventions in the aortoiliac segment in 2016 was 34.7% – 4.056 operations. Angioplasty and stenting of the femoral arteries were performed in 3662 cases, popliteal arteries – in 1408 [3]. The results of endovascular interventions are impressive, but the problem of postoperative thrombotic complications remains very relevant. According to the study of K. Katsanos et al. during the first year, up to 12.5% of drug-eluting stents and 1.4% uncoated are thrombosed [4].

An important role in the development of thrombotic complications after reconstructive and restorative interventions is played by the coagulation system of hemostasis. The effect of the vascular-platelet link and extrinsic coagulation pathway on the processes of thrombus formation in patients with peripheral artery disease is widely covered and investigated, which facilitated the introduction of a variety of antithrombotic drugs into angiology and vascular surgery [5]. The connection between the intrinsic pathway of the coagulation cascade from the position of thrombotic complications in patients with this pathology has not been studied sufficiently, the results of the conducted studies are contradictory [6]. The main factors of the intrinsic pathway of coagulation are VIII and IX, XI and XII. These 4 factors, phospholipases, Ca^{2+} ions, kininogen and prekallikrein are necessary for activation of the internal blood coagulation cascade [7].

The endothelium and its metabolites have great importance in maintaining the balance between coagulation and anticoagulation systems of the blood [8]. Numerous studies conducted in recent decades have been devoted to the study of the endothelial dysfunction from the point of production of nitric oxide, pro- and anti-inflammatory mediators, evaluation of platelet activity and factors of the extrinsic clotting pathway, while the role of hemostatic markers of the endothelial dysfunction, as well as their interrelation with factors of the intrinsic cascade of coagulation remains completely unexplored in patients with atherosclerosis. Normally, the athrombogenic factors of the vascular wall inhibit thrombinogenesis, inactivate procoagulants, activate fibrinolysis, inhibit the adhesion and aggregation of platelets, but do not interfere with hemostasis in vascular damage, thus limiting the process of thrombosis. It is interesting that VIII factor is produced not only in sinusoidal cells of the liver, but also in the extrahepatic endothelium, which is confirmed by the interrelation of the hemostatic system with the state of the endothelium of the vascular wall [9]. During surgery, the endothelium inevitably traumatizes, leading to its dysfunction. One of the main markers of dysfunction of the endothelium, directly involved in hemostasis, is the von Willebrand factor (VWF) [10]. Thus, the activity of internal cascade factors and their relationship with hemostatic markers of the endothelial dysfunction in patients with PAD and the impact on their dynamics of surgical intervention remain unclear.

Objective. To assess the activity of intrinsic coagulation cascade factors of coagulation and hemostatic markers of endothelial dysfunction in patients with peripheral artery disease (PAD) before and after endovascular treatment.

Methods

The study included 80 patients with PAD in the stage IIB-III of the disease according to

Fontaine classification, who underwent treatment on the basis of Ryazan Regional Clinical Cardiac Dispensary.

The criteria for inclusion in the study were the following: men or women older than 40 years; the presence of peripheral artery disease.

Exclusion criteria were men or women under 40, chronic ischemia of the lower limbs of another etiology (Buerger's disease, aortoarteritis, etc.), active cancer or remission period of less than 5 years; decompensated diabetes mellitus.

Patients signed informed consent about the participation in the study, possible publication of materials highlighting the features of their disease and the methods of diagnosis and treatment applied, about guarantees of confidentiality when placing them in print and electronic publications. The study was approved by a local ethics committee. 40 patients with PAD were subjected to endovascular interventions on the aortofemoropopliteal segment (group A) and 40 patients underwent conservative treatment (group B, control group).

The decision on the choice of the optimal type of treatment was made by a group consisting of vascular surgeon, X-ray and endovascular surgeon, angiologist and cardiologist, based on the individual anatomical and physiological characteristics of the patients, laboratory and instrumental research methods.

The main indications are defined in accordance with the transatlantic consensus TASCII – (TransAtlantic Inter-Society Consensus) and are reflected in the Recommendations of the Russian Society of Angiologists and Vascular Surgeons (2013). The groups were comparable in age, gender composition. Clinical characteristics of patients are presented in Table 1.

According to the design of the study, samples of peripheral venous blood were taken from patients in group A before and 3 months after surgery, and in patients in group B, when included in the study. The following parameters of hemostasis were analyzed: the activity of factors VIII, IX, XI, VWF, the level of nitric oxide II and protein C (PrC). The instrumental examination methods included Doppler ultrasonography with the calculation of the ankle-brachial index (ABI) (GE Vivid Five apparatus, Angiodin-PC sensor), ultrasonic duplex scanning (Sono Scape S20 Pro) and angiographic examination (Axiom Artis apparatus) of the vessels of the lower limbs in all patients when included in the study according to the indications in accordance with the practice of managing patients accepted in vascular surgery.

Table 1

Clinical characteristics of patients

Indicator, units of measure	Group A	Group B
Age, years (M±σ).	63.9±7.93 years	59.8±8.34
Men, n (%)	30 (75%)	36 (90%)
Women, n (%)	10 (25%)	4 (10%).
Stage of chronic lower limb ischemia		
II B st., n (%)	10 (25%)	32 (80%)
III st., n (%)	30 (75%)	8 (20%)
Concomitant diseases and conditions		
Diabetes mellitus type 2, n (%)	11 (27.5%)	4 (10%)
Cardiac ischemia, n (%)	20 (50%)	20 (50%)
Arterial hypertension, n (%)	25 (62.5%)	20(50%)
Postinfarction cardiosclerosis, n (%)	11 (27.5%)	8 (20%)
Atrial fibrillation, n (%)	1 (2.5%)	3 (7.5 %)
Aorto-coronary bypass surgery, n (%)	1 (2.5%)	-
Percutaneous coronary angioplasty, n (%)	2 (5%)	-
Smoking in the anamnesis, n (%)	30 (75%)	29 (72.5%)
Initial anatomical and angiographic characteristics of patients		
Aorto-iliac segment, n (%)	17 (42.5%)	13 (32.5%)
Thigh-popliteal segment,n (%)	23 (57.5%)	27 (67.5%)
Patients' distribution by type of endovascular intervention		
TLBAP, n (%)	20 (50%)	Conservative therapy
EP EIA , n (%)	9 (22.5%)	
EP CIA, n (%)	5 (12.5%)	
EP FA, n (%)	3 (7.5%)	
TLBAP, n (%)	3 (7.5%)	

Notes: TLBAP – transluminal balloon angioplasty, EP – endoprosthetics, FA – femoral artery, EIA – external iliac artery, CIA – common iliac artery.

Group A patients were then subjected to transluminal balloon angioplasty/stenting (TLBAP) of the iliacfemoropopliteal segment arteries in accordance with the recommendations in the transatlantic consensus document (TASC-II). After surgery, patients were on dual antiplatelet therapy (clopidogrel and drugs of the acetylsalicylic acid group). The volume of conservative therapy in patients in Group B corresponded to the "National Recommendations for the Treatment of Peripheral Artery Diseases" of 2013, which included hypocholesterolemic agents, disaggregants, and drugs that improve blood rheology.

Patients of the two groups 3 and 6 months after inclusion in the study were subjected to a general examination, measurement of the ABI and USDS of the arteries of the lower limbs to assess thrombotic complications, the patency of the reconstruction zone and the progression of the disease. The primary endpoint was the development of thrombotic complications in patients enrolled in the study. As the secondary end points one regarded the safety of the limb in a patient or his death.

Determination of the activity of VIII, IX, XI factors was carried out using a clotting haemostasis method using the optical, semiautomatic coagulometer SYSMEXCA 50 (Japan), PRC chromogenic with substrate on the automatic coagulometer SYSMEXCA 660 (Japan), VWF by agglutination of platelets in the presence of VW factor and ristocytin A – manual technique, metabolites of NO – photocolorimetric method [11].

Statistics

Statistical analysis of the data was carried out using the STATISTICA 10.0 statistical software package. The analysis of the data was studied for the correspondence of the distribution of the value of the test feature to the law of normal distribution. To assess the normality of the sample distribution, the Shapiro-Wilk test was used. In connection with the deviation from the normal distribution, nonparametric tests were used for further analysis, the data were presented in the form of a median and quartiles. To assess the statistical differences between two independent samples, the Mann-Whitney U test was used to compare two dependent samples – the Wilcoxon Criterion, a correlation analysis was performed using the Spearman coefficient. Differences were considered statistically significant at $p \leq 0.05$.

Results

In Group A patients, the mean values of the activity of VIII, IX, XI factors and VWF before surgery were increased in comparison with the norm. After 3 months, an even greater increase in the activity of VIII, IX, XI factors was observed, an increased level of VWF persisted with a decrease in NO metabolites. The level of PrC was within the normal range both before and after the operation. Statistically significant changes were obtained for factor VIII (p=0.01), IX factor (p=0.005), XI factor (p=0.014), NO (p=0.048).

In patients of group B, the values of activity of VWF and IX factor were increased, at a normal level of metabolites of NO, PrC, VIII, XI factors in comparison with the norm. In comparison with the indices of group A, fairly important were the differences in the levels of VWF (p=0.006) and VIII (p = 0.01) factors, NO metabolites (p=0.046) before the operation, VWF (p=0.0001), VIII (p=0.003), IX (p=0.029), XI (p=0.0002) factors and NO metabolites (p=0.0002) after the operation (Table 2).

30 (75%) of 40 patients in group A had stage III of the disease according to the Fontaine classification, which was one of the possible causes of the prothrombogenic state of the hemostasis

Table 2

Laboratory indicators of hemostasis

Group	Indicators	PrC	VWF	NO	VIII	IX	XI
	Norm	70-130%	70-150%	76,3 mkmol/l	70-150%	70-150%	70-130%
Group B	Median	105.9	300	71.9	133.9	201.8	124.1
	Lower Quartile	94.7	160	50	96.6	122.3	99.8
	Upper Quartile	114.4	400	95.4	156.9	255.2	149
Group A (figures before intervention)	Median	105	600	65	157	180	156
	Lower Quartile	86	300	48	128	134	92
	Upper Quartile	114	1200	72	210	237	195
Group A (figures 3 months after intervention)	Median	103	600	52	184	218	181
	Lower Quartile	92	300	35	138	156	119
	Upper Quartile	127	800	69	271	297	226

system against the background of normal PrC level and reduced NO. K. Cassar et al. showed that the level of VWF in patients with PAD exceeds that of healthy patients, and the degree of increase in activity of VWF directly correlates with the severity of atherosclerotic process [12].

A direct correlation is observed between the activity of VWF and VIII factor (r=+0.534) in Group A, before surgery; after the intervention – the reverse between NO and VWF (r=-0.445).

In group B, a direct correlation was found out between the activity of factor VIII and VWF (r=+ 0.427), IX factor (r=+0.620), XI factor (r=+ 0.626), and patient's age (r=+0.426).

Six months after the endovascular intervention, the primary permeability of the reconstruction zone, according to the data of the USDS of the arteries of the lower limbs was 79%. In 6 (15.7%) patients, according to the data of the USDS of the arteries of the lower limbs, after 6 months, restenosis of the reconstruction zone was revealed, which required a repeated endovascular intervention with a positive effect. In 2 (5%) patients after stenting of CIA and EIA, thrombosis of the intervention zone was detected. In the first case, alloplastics of FA with thrombectomy from the arteries of the ileum-femoral segment of the affected limb with a positive effect was performed according to the emergency indications. In 1 (2.5%) patients the progression of atherosclerotic lesion of the contralateral lower limb developed, which required the endovascular reconstruction. Statically significant increase in VWF activity (p=0.023) and a decrease in the NO metabolites index (p=0.003) were noted before the operation in Group A patients with subsequent restenosis of the reconstruction zone. During the follow-up period, no thrombotic complications were detected in group B.

Discussions

At present, there is no doubt about the relationship between the processes of development of atherosclerosis and the disruption of the blood coagulation system. Hypercoagulation can be not only a consequence of atherosclerosis, but also an active participant in its progression [13]. In our study, the increased values of the activity of VWF, VIII, IX, XI factors before an endovascular intervention reflect the prothrombogenic state of the hemostatic system of patients with PAD.

The operation promotes a shift towards hypercoagulation and disruption of endothelial functional activity, as evidenced by an increased activity of VWF, VIII, IX, XI factors and decreased – NO metabolites.

The revealed correlation links can be explained by the joint circulation of the VIII factor in combination with VWF, which protects it from the inactivation of PrC [14]. In patients of older age groups, there is a shift in the hemostatic system toward hypercoagulability. The interrelationships of VIII, IX, XI factors confirm the theory of the sequence of proteolytic reactions of the coagulation cascade [7]. NO adversely affects the secretion of VWF. The classical effects of NO are caused by the activation of soluble guanylate cyclase, the generation of cyclic GMP (cGMP), and cGMP-dependent protein kinase-1. Its activation leads to inhibition of agonist-induced mobilization of calcium and, consequently, secretion of VWF [15].

Conclusions

Analysis of the initial state of the hemostasis system in patients with peripheral artery disease allows concluding that there are pronounced changes: the development of a hypercoagulable state against the background of a normal anticoagulation potential. Operative intervention provides an even greater shift towards hypercoagulation and violation of the functional state of the endothelium.

Evaluation of the indices of the activity of intrinsic cascade coagulation factors and markers of endothelial dysfunction in dynamics, taking into account clinical manifestations and instrumental diagnostic methods, can contribute to an assessment of the severity of the disease, its prognosis, adequate medication and surgical correction.

Funding

The work was carried out under the grant of the European Society of Vascular Surgery — European Society for Vascular Surgery Research Grant 2016: Impact of intrinsic coagulation pathway factors activity and hemostatic markers of endothelial dysfunction on thrombotic complications in patients with atherosclerotic peripheral arterial disease.

The authors did not receive financial support from the drug manufacturers.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethics Committee approval

The study was approved by the Ethics Committee of Ryazan State Medical University named after Academician I.P. Pavlov.

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Информация о статье

Получена 20 декабря 2017г.
Принята в печать 16 июля 2018 г.
Доступна на сайте 31 октября 2018 г.

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Article history

Arrived 20 December 2017
Accepted for publication 16 July 2018
Available online 31 October 2018